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DETERMINATION OF URINE METABOLITE LEVELS FOLLOWING INHALATION O--ETC(U)
AUG 78 J A GERE, R E BOLDT

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UNITED STATES ARMY ENVIRONMENTAL HYGIENE AGENCY

ABERDEEN PROVING GROUND, MD 21010

DETERMINATION OF URINE METABOLITE LEVELS FOLLOWING INHALATION OF THE INSECTICIDE PERMETHRIN IN RATS
STUDY NO. 75-53-0053-79
MAY - AUGUST 1978

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Permethrin Metabolic Rat
SBP-1513 Urine

(+ or -)

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The Pyrethroid insecticide Permethrin, 3-phenoxybenzyl-(±)-cis, trans-3-(2,2 dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate, was administered to rats as an aerosol. Metabolite studies of the urine showed the presence of significant quantities of Permethrin metabolites for several days following exposure. The pattern of metabolite excretion indicates an extremely efficient mechanism for the metabolism and excretion of this compound.

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DEPARTMENT OF THE ARMY
U. S. ARMY ENVIRONMENTAL HYGIENE AGENCY
ABERDEEN PROVING GROUND, MARYLAND 21010

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24 JAN 1979

HSE-LR-B/WP

SUBJECT: Determination of Urine Metabolite Levels Following Inhalation of the Insecticide Permethrin in Rats, Study No. 75-53-0053-79, May-August 1978

Executive Secretary
Armed Forces Pest Control Board
Forest Glen Section, WRAMC
Washington, DC 20012

A summary of the pertinent findings of the inclosed report follows:

The pattern of primary excretion in rats of Permethrin during and following inhalation exposure was measured. The urine was found to contain metabolite that quickly reaches a dose related concentration permitting measurement of adsorption and excretion rates.

FOR THE COMMANDER:

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DEPARTMENT OF THE ARMY
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DETERMINATION OF URINE METABOLITE LEVELS FOLLOWING INHALATION OF THE INSECTICIDE PERMETHRIN IN RATS
STUDY NO. 75-53-0053-79
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1. AUTHORITY.

a. Memorandum of Understanding between the Department of the Army, Office of The Surgeon General, the US Army Health Services Command, the US Army Environmental Hygiene Agency, the Armed Forces Pest Control Board (AFPCB), and the US Department of Agriculture, effective December 1970 with Amendment No. 1, effective August 1974.

b. Letter, AFPCB, Armed Forces Pest Control Board, 21 October 1975, subject: Request for Toxicological Evaluation.

c. Letter, AFPCB, Armed Forces Pest Control Board, 5 April 1977, subject: Request for Toxicological Evaluation.

2. REFERENCES.

a. Interim Report, HSE-LT, this Agency, Preliminary Assessment of Relative Toxicity of Candidate Insect Repellent AI3-29158, 3-Phenoxybenzyl cis/trans 2,2-dimethyl-3-(2,2-dichlorovinyl) cyclopropanecarboxylate Study No. 51-031-76, December 1975 - April 1976.

b. Report, HSE-LT, this Agency, Toxicological Evaluation of 3-(phenoxyphenyl) methyl (±)-cis, trans-3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate (Permethrin), Study No. 51-0831-78, December 1975 - April 1977.

c. Toxicology Division Procedural Guide, USAEHA, 1972, revised 1976.

3. PURPOSE. The purpose of this investigation was to determine the pattern of Permethrin metabolite excretion in the urine of rats which were being used in an inhalation toxicology study. The results of the toxicology study will be detailed in a separate USAEHA report. Results of the present investigation are for advising the AFPCB on the possible hazard in use of this compound with human subjects.

The use of company names or their product does not imply indorsements by the US Army, but is intended only to assist in identification of a specific compound.

4. GENERAL.

a. Permethrin [3-phenoxybenzyl-(±)-cis, trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate], a synthetic pyrethroid, is an amber colored liquid having a specific gravity of 1.2, melting point of 35°F and boiling point of 220°F. It is soluble in organic solvents (acetone, hexane). The sample studied was SBP-1513, lot No. RAX-6*.

b. Detailed descriptions of the inhalation exposures will be reported elsewhere[1]. Four male Sprague-Dawley rats per group were exposed to Permethrin aerosols at concentations of 0, 125, 250, and 500 mg/M^3. The animals were exposed for 6 hours per day, 5 days per week for 13 weeks. No exposures were performed on Saturdays or Sundays. The metabolite excretion determinations were begun on Monday of the thirteenth week of exposure.

c. The animals were removed from the inhalation chambers or holding cages (Saturday and Sunday), where they were individually caged, and placed into individual metabolism cages. Urine was collected in plastic cups until 8:00 AM the following morning, when the animals were again placed in inhalation chambers or holding cages.

d. The volume of the individual urine samples was measured each morning and the concentration of 3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (ClVA) was determined by the as yet unpublished procedure of Cridland and Weatherley[2]. Excreted almost exclusively as the glucuronide and sulfate esters, this metabolite is known to appear rapidly in the urine of animals exposed to Permethrin,[3,4] and to represent over 50% of an administrered oral dose[4]. The method of analysis includes the enzymatic hydrolysis of the metabolite, esterification and determination by gas chromatography. Authentic ClVA† was used for standarization.

e. Literature cited in this report is shown in the Appendix.

5. FINDINGS.

a. Extraction of ClVA, after enzymatic hydrolsis of the metabolite, was accomplished with hexane followed by centrifugation to separate the phases. Phase separation was difficult because of an apparent increase in lipid content of the rat urine, becoming impossible in those urine samples collected within 24 hours after exposure of the animals to the highest dose of Permethrin. Phases were well resolved in urine from rats receving lower doses, or on Saturday or Sunday when the animals were not exposed to Permethrin.

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* SBP-1513 is a company designation of CPC International, Inc., S.B. Penick and Co., 160 Church Street, NY, NY 10007.
† Obtained from Dr. James Hubbell, Burroughs-Wellcome Co., Research Triangle Park, NC 27709.

b. Permethrin metabolite concentration analyses were performed on the urine collected as described. The results of analyses are shown in the Table and Figure. The concentration of Permethrin metabolite increased during the week, reaching a maximum on Thursday and Friday. A dramatic decrease took place on Saturday, when no exposure occurred; a further decrease was apparent on Sunday. This pattern was true for all dose levels, animals receiving the highest dose excreted approximately three times more of the metabolite than those exposed to the lower dose levels. Control animals uniformly excreted a very low (below 20 g/day) quantity of the metabolite.

TABLE. Average C1VA Content of Rat Urine (g/Sample/Rat) 13th Week.

	500 mg/M^3	250 mg/M^3	125 mg/M^3	0 mg/M^3
Monday	2140 ± 172	401 ± 67	365 ± 16	< 20
Tuesday	2360 ± 401	540 ± 100	550 ± 4	< 20
Wednesday	2843 ± 343	415 ± 30	788 ± 76	< 20
Thursday	2879 ± 190	663 ± 63	1058 ± 124	< 20
Friday	2777 ± 60	827 ± 24	959 ± 35	< 20
Saturday	884 ± 88	446 ± 37	195 ± 19	< 20
Sunday	598 ± 36	329 ± 26	229 ± 15	< 20

6. DISCUSSION. Administration of the pyrethroid insecticide, Permethrin, by inhalation caused a gradual increase in the rate of urinary Permethrin metabolite excretion, reaching a maximum in 3-4 days. It is especially interesting that the urine concentration rapidly fell after inhalation exposures were discontinued. Animals receving the highest dose of Permethrin excreted approximately three times as much of the metabolite as those receiving the lower doses. Only 2 days after the cessation of exposures, the excretion rate of all animals had dropped to roughly the same level. These data indicate that the animals possess a very efficient mechanism for the detoxification and excretion of Permethrin. This permits a drop in the excretion level to only 20-45 percent of the test levels by the second day after the end of the exposure period. Support for this view comes from a recent report[5] on the purification and characterization, from rat liver microsomes, of the enzyme pyrethroid carboxyesterase, which hydrolyzes esters of chrysanthemumic acid such as Permethrin.

Note: Urine was collected from the time inhalation was discontinued each afternoon until 8AM the following morning, i.e. the designation "Mon" represents collection from Monday afternoon thru Tuesday morning.

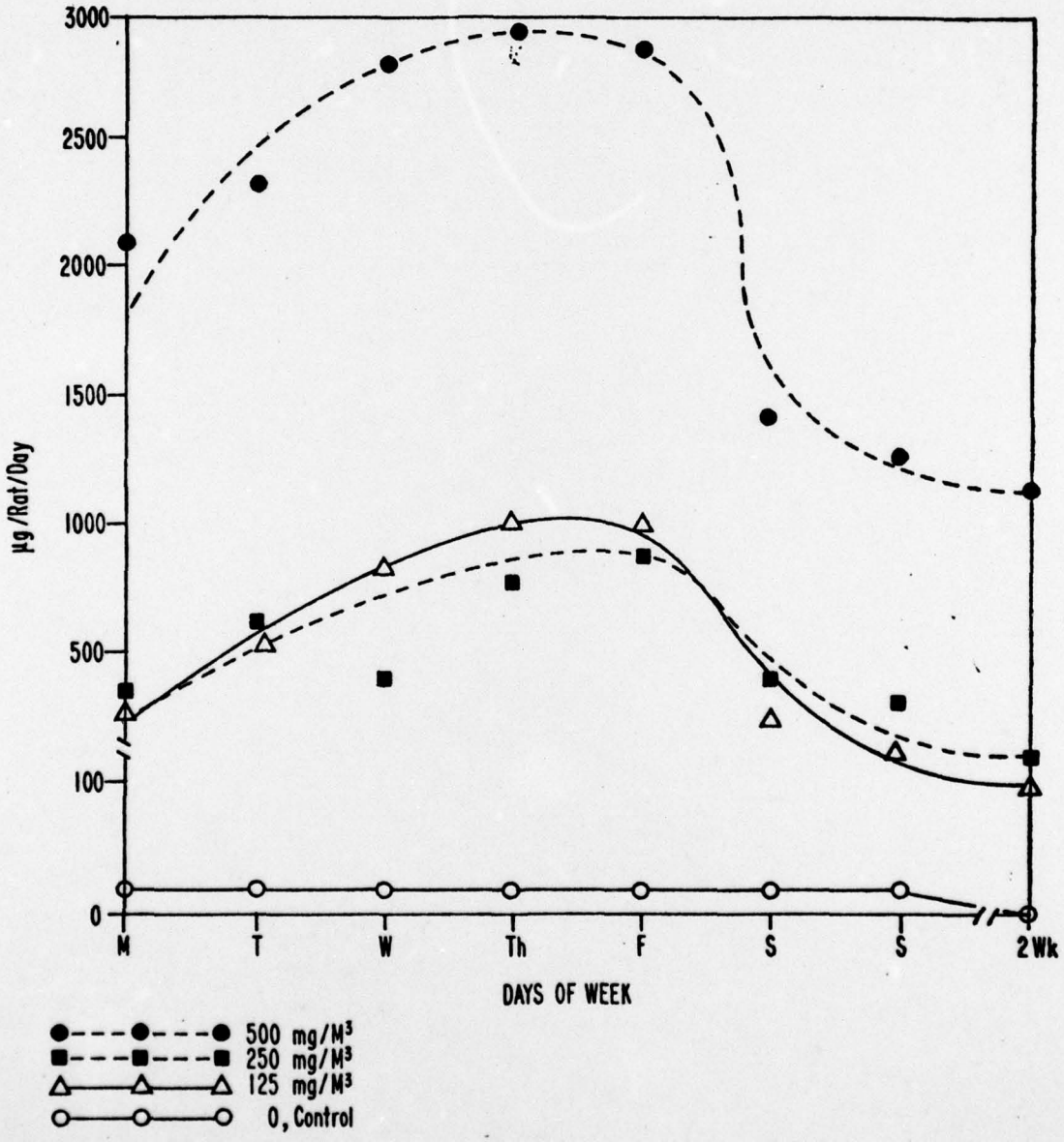

FIGURE I: PERMETHRIN CONTENT OF RAT URINE, µg/RAT/DAY

7. CONCLUSION. The urine of rats exposed to Permethrin by inhalation has been found to contain a pyrethroid metabolite which very quickly reaches a dose-related concentration showing that an inhaled aerosol of the pesticide is readily absorbed, metabolized and excreted in the urine.

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APPENDIX

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